



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/GB97/01360 (22) International Filing Date: 20 May 1997 (20.05.97) (30) Priority Data:  <table border="0"> <tr> <td>9610506.9</td> <td>20 May 1996 (20.05.96)</td> <td>GB</td> </tr> <tr> <td>9623234.3</td> <td>7 November 1996 (07.11.96)</td> <td>GB</td> </tr> <tr> <td>9626883.4</td> <td>24 December 1996 (24.12.96)</td> <td>GB</td> </tr> <tr> <td>9708071.7</td> <td>22 April 1997 (22.04.97)</td> <td>GB</td> </tr> </table> <p>(71) Applicant (for all designated States except US): CHIRO-SCIENCE LIMITED [GB/GB]; Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): DYKE, Hazel, Joan [GB/GB]; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). MONTANA, John, Gary [GB/GB]; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). (74) Agent: GILL JENNINGS &amp; EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).</p> </p>		9610506.9	20 May 1996 (20.05.96)	GB	9623234.3	7 November 1996 (07.11.96)	GB	9626883.4	24 December 1996 (24.12.96)	GB	9708071.7	22 April 1997 (22.04.97)	GB	<p>(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
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<p>(54) Title: QUINOLINE SULFONAMIDES AS TNF INHIBITORS AND AS PDE-IV INHIBITORS</p> <p>(57) Abstract</p> <p>A compound of general formula (i), wherein R is H, halogen or alkyl; R<sub>1</sub> represents OH, alkoxy optionally substituted with one or more halogens, or thioalkyl; R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are the same or different and are each H, R<sub>7</sub>, OR<sub>11</sub>, COR<sub>7</sub>, C(=NOR<sub>7</sub>)R<sub>7</sub>, alkyl-C(=NOR<sub>7</sub>)R<sub>7</sub>, alkyl-C(=NOH)R<sub>7</sub>, C(=NOH)R<sub>7</sub>, halogen, CF<sub>3</sub>, CN, CO<sub>2</sub>H, CO<sub>2</sub>R<sub>11</sub>, CONH<sub>2</sub>, CONHR<sub>7</sub>, CON(R<sub>7</sub>)<sub>2</sub>, NR<sub>9</sub>R<sub>10</sub> or CONR<sub>12</sub>R<sub>13</sub> where NR<sub>12</sub>R<sub>13</sub> is a heterocyclic ring optionally substituted with one or more R<sub>15</sub>; R<sub>5</sub> represents H, arylalkyl, heteroarylalkyl, S(O)<sub>m</sub>R<sub>11</sub> or alkyl optionally substituted with one or more substituents chosen from hydroxy, alkoxy, CO<sub>2</sub>R<sub>8</sub>, SO<sub>2</sub>NR<sub>12</sub>R<sub>13</sub>, CONR<sub>12</sub>R<sub>13</sub>, CN, carbonyl oxygen, NR<sub>9</sub>R<sub>10</sub>, COR<sub>11</sub> and S(O)<sub>n</sub>R<sub>11</sub>; R<sub>6</sub> represents aryl, heteroaryl, arylalkyl or heteroarylalkyl. The compounds can be used to treat disease states, for example disease states associated with proteins that mediate cellular activity, for example by inhibiting tumour necrosis factor and/or by inhibiting phosphodiesterase IV.</p> <div style="text-align: right;"> <p>(i)</p> </div> <div style="text-align: center; margin-top: 20px;"> </div>														

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## QUINOLINE SULFONAMIDES AS TNF INHIBITORS AND AS PDE-IV INHIBITORS

Field of the Invention

The present invention relates to novel quinolines, and to their formulation and use as pharmaceuticals.

5 Background of the Invention

Japanese Patent Publication 2-184673 discloses quinolinesulphonamides.

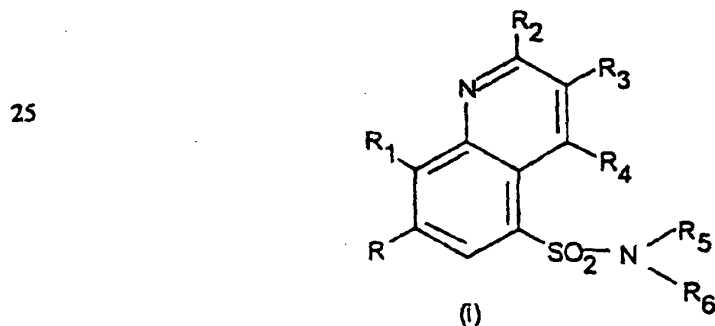
US-A-4910193 discloses quinolinesulphonamides, in which the sulphonamide nitrogen is substituted by a variety of bridged saturated ring systems, as medicaments suitable for the treatment of serotonin-induced gastrointestinal disturbances.

10 US-A-4857301 and US-A-5340811 disclose quinolinesulphonamides in the treatment of asthma, respectively as bronchodilators and as anti-allergic compounds.

Phosphodiesterases (PDE) and Tumour Necrosis Factor (TNF), their modes of action and the therapeutic utilities of inhibitors thereof, are described in WO-A-9636595, WO-A-9636596 and WO-A-9636611, the contents of which are incorporated herein by  
15 reference. The same documents disclose sulphonamides having utility as PDE and TNF inhibitors.

Summary of the Invention

This invention is based on the discovery of novel compounds that can be used to treat disease states, for example disease states associated with proteins that mediate  
20 cellular activity, for example by inhibiting tumour necrosis factor and/or by inhibiting phosphodiesterase IV. According to the invention, the novel compounds are of formula (i):



wherein R is H, halogen or alkyl;

$R_1$  represents OH, alkoxy optionally substituted with one or more halogens, or thioalkyl;

$R_2$ ,  $R_3$  and  $R_4$  are the same or different and are each H,  $R_7$ ,  $OR_{11}$ ,  $COR_7$ ,  $C(=NOR_7)R_7$ , alkyl- $C(=NOR_7)R_7$ , alkyl- $C(=NOH)R_7$ ,  $C(=NOH)R_7$ , halogen,  $CF_3$ , CN,  $CO_2H$ ,  $CO_2R_{11}$ ,  $CONH_2$ ,  $CONHR_7$ ,  $CON(R_7)_2$ ,  $NR_9R_{10}$  or  $CONR_{12}R_{13}$  where  $NR_{12}R_{13}$  is a heterocyclic ring (such as morpholine or piperidine) optionally substituted with one or more  $R_{15}$ ;

$R_5$  represents H, arylalkyl, heteroarylalkyl,  $S(O)_mR_{11}$  or alkyl optionally substituted with one or more substituents chosen from hydroxy, alkoxy,  $CO_2R_8$ ,  $SO_2NR_{12}R_{13}$ ,  $CONR_{12}R_{13}$ , CN, carbonyl oxygen,  $NR_9R_{10}$ ,  $COR_{11}$  and  $S(O)_nR_{11}$ ;

$R_6$  represents aryl, heteroaryl, arylalkyl or heteroarylalkyl;

in  $R_5$  and/or  $R_6$ , the aryl/heteroaryl portion is optionally substituted with one or more substituents alkyl- $R_{14}$  or  $R_{14}$ ;

$R_7$  represents  $R_{11}$  optionally substituted at any position with (one or more)  $R_{16}$ ;

$R_8$  represents H, alkyl, cycloalkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

$R_9$  represents H, aryl, heteroaryl, heterocyclo, alkyl, cycloalkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl, alkylcarbonyl, alkoxy carbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclosulphonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclocarbonyl or alkylsulphonyl;

$R_{10}$  represents H, aryl, heteroaryl, heterocyclo, alkyl, cycloalkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

$R_{11}$  represents alkyl, cycloalkyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl or heterocycloalkyl;

$R_{12}$  and  $R_{13}$  are the same or different and are each H or  $R_{11}$ , or  $NR_{12}R_{13}$  represents a heterocyclic ring as defined above;

$R_{14}$  represents alkyl (optionally substituted by one or more halogens), cycloalkyl, aryl, heteroaryl, heterocyclo, hydroxy, alkoxy (optionally substituted by one or more halogens), thioalkyl, aryloxy, heteroaryloxy, heterocycloxy, arylalkyloxy, heteroarylalkyloxy, heterocycloalkyloxy,  $CO_2R_8$ ,  $CONR_{12}R_{13}$ ,  $SO_2NR_{12}R_{13}$ , halogen, -CN,  $-NR_9R_{10}$ ,  $COR_{11}$ ,  $S(O)_nR_{11}$ , or (where appropriate) carbonyl oxygen;

$R_{15}$  represents alkyl, arylalkyl or heteroarylalkyl;

$R_{16}$  represents alkyl, OH,  $OR_{11}$ ,  $NR_9R_{10}$ , CN,  $CO_2H$ ,  $CO_2R_{11}$ ,  $CONR_{12}R_{13}$  or  $COR_{11}$ ;

m represents 1-2; and

n represents 0-2;

5 and pharmaceutically-acceptable salts.

Combinations of substituents and/or variables are only permissible if such combinations result in stable compounds.

#### Description of the Invention

Suitable pharmaceutically-acceptable salts are pharmaceutically-acceptable base  
10 salts and pharmaceutically-acceptable acid addition salts. Certain of the compounds of formula (i) which contain an acidic group form base salts. Suitable pharmaceutically-acceptable base salts include metal salts, such as alkali metal salts for example sodium salts, or organic amine salts such as that provided with ethylenediamine.

Certain of the compounds of formula (i) which contain an amino group form acid  
15 addition salts. Suitable acid addition salts include pharmaceutically-acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically-acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methanesulphate,  $\alpha$ -ketoglutarate,  $\alpha$ -glycerophosphate and glucose-1-phosphate. The pharmaceutically-acceptable salts of the  
20 compounds of formula (i) are prepared using conventional procedures.

It will be appreciated by those skilled in the art that some of the compounds of formula (i) may exist in more than one tautomeric form. This invention extends to all tautomeric forms.

It will be appreciated that the compounds according to the invention can contain  
25 one or more asymmetrically substituted atoms. The presence of one or more of these asymmetric centers in a compound of formula (i) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers, and diastereoisomers and mixtures including racemic mixtures thereof.

When used herein the term alkyl whether used alone or when used as a part of  
30 another group includes straight and branched chain alkyl groups containing up to 6 atoms. Alkoxy means an alkyl-O- group in which the alkyl group is as previously described. Aryloxy means an aryl-O- group in which the aryl group is as defined below.

Heteroaryloxy means a heteroaryl-O- group and heterocyclooxy means a heterocyclo-O- group in which the heteroaryl and heterocyclo group are as defined below. Alkylamino means an alkyl-N- group in which the alkyl group is as previously defined, arylamino means aryl-N- and heteroarylamino means an heteroaryl-N- group (aryl and heteroaryl defined below). Thioalkyl means an alkyl-S-group. Cycloalkyl includes a non-aromatic cyclic or multicyclic ring system of about 3 to 10 carbon atoms. The cyclic alkyl may optionally be partially unsaturated. Aryl indicates carbocyclic radicals containing about 6 to 10 carbon atoms. Arylalkyl means an aryl-alkyl- group wherein the aryl and alkyl are as described herein. Heteroarylalkyl means a heteroaryl-alkyl group and heterocycloalkyl means a heterocyclo-alkyl group. Alkylcarbonyl means an alkyl-CO- group in which the alkyl group is as previously described. Arylcarbonyl means an aryl-CO- group in which the aryl group is as previously described. Heteroarylcarbonyl means a heteroaryl-CO- group and heterocyclocarbonyl means a heterocyclo-CO- group. Arylsulphonyl means an aryl-SO<sub>2</sub>- group in which the aryl group is as previously described. Heteroarylsulphonyl means a heteroaryl-SO<sub>2</sub>- group and heterocyclosulphonyl means a heterocyclo-SO<sub>2</sub>- group. Alkoxy carbonyl means an alkoxy-CO- group in which the alkoxy group is as previously described. Alkylsulphonyl means an alkyl-SO<sub>2</sub>- group in which the alkyl group is as previously described. Carbonyl oxygen means a -CO- group. It will be appreciated that a carbonyl oxygen can not be a substituent on an aryl or heteroaryl ring. Carbocyclic ring means about a 5 to about a 10 membered monocyclic or multicyclic ring system which may saturated or partially unsaturated. Heterocyclo ring means about a 5 to about a 10 membered monocyclic or multicyclic ring system (which may saturated or partially unsaturated) wherein one or more of the atoms in the ring system is an element other than carbon chosen from amongst nitrogen, oxygen or sulphur atoms. Examples include morpholine and piperidine. Heteroaryl means about a 5 to about a 10 membered aromatic monocyclic or multicyclic hydrocarbon ring system in which one or more of the atoms in the ring system is an element other than carbon, chosen from amongst nitrogen, oxygen or sulphur; if desired, a N atom may be in the form of an N-oxide. Heterocyclo means about a 5 to about a 10 membered saturated or partially saturated monocyclic or multicyclic hydrocarbon ring system in which one or more of the atoms in the ring system

is an element other than carbon, chosen from amongst nitrogen, oxygen or sulphur. Halogen means fluorine, chlorine, bromine or iodine.

Compounds of the invention are useful for the treatment of TNF mediated disease states. "TNF mediated disease or disease states" means any and all disease states in which  
5 TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance, is a major component, and whose production or action is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF. As  
10 TNF- $\beta$  (also known as lymphotoxin) has close structural homology with TNF- $\alpha$  (also known as cachectin), and since each induces similar biologic responses and binds to the same cellular receptor, both TNF- $\alpha$  and TNF- $\beta$  are considered to be inhibited by compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically indicated otherwise.

This invention relates to a method for mediating or inhibiting the enzymatic activity  
15 or catalytic activity of PDE IV in a mammal in need thereof and for inhibiting the production of TNF in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (i) or a pharmaceutically-acceptable salt thereof.

PDE IV inhibitors are useful in the treatment of a variety of allergic and  
20 inflammatory diseases, including: asthma, chronic bronchitis, chronic obstructive airways disease, atopic dermatitis, atopic eczema, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, psoriasis, Bechet's disease, erythematosis, anaphylactoid purpura nephritis, joint inflammation, arthritis, rheumatoid arthritis and other arthritic conditions such as  
25 rheumatoid spondylitis and osteoarthritis, septic shock, sepsis, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus and conditions associated with cerebral metabolic inhibition, such as cerebral senility, senile dementia (Alzheimer's disease),  
30 memory impairment associated with Parkinson's disease, depression and multi-infarct dementia. PDE IV inhibitors are also useful in conditions ameliorated by neuroprotectant activity, such as cardiac arrest, stroke and intermittent claudication. PDE IV inhibitors

may be useful in the treatment of tardive dyskinesia, ischaemia and Huntingdon's disease. Additionally, PDE IV inhibitors could have utility as gastroprotectants. A special embodiment of the therapeutic methods of the present invention is the treatment of asthma.

- 5       The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (i). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, such as, but not limited to, *Herpes*  
10   *zoster* and *Herpes simplex*.

This invention more specifically relates to a method of treating a mammal, afflicted with a human immunodeficiency virus (HIV), which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (i) or a pharmaceutically-acceptable salt thereof.

- 15       The compounds of this invention may also be used in association with the veterinary treatment of animals, other than humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to feline immunodeficiency virus  
20   (FIV) or other retroviral infection such as equine infectious anaemia virus, caprine arthritis virus, visna virus, maedi virus and other lentiviruses.

The compounds of this invention are also useful in treating parasite, yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. A preferred disease state for treatment is fungal meningitis.

- 25       Compounds of the invention may also suppress neurogenic inflammation through elevation of cAMP in sensory neurones. They are, therefore, analgesic, anti-tussive and anti-hyperalgesic in inflammatory diseases associated with irritation and pain.

- The compounds of formula (i) are preferably in pharmaceutically-acceptable form. By pharmaceutically-acceptable form is meant, *inter alia*, of a pharmaceutically-acceptable  
30   level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. A pharmaceutically-

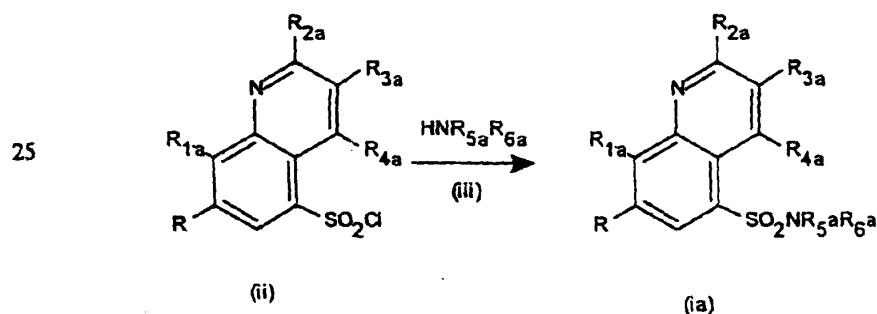


acceptable level of purity will generally be at least 50% excluding normal pharmaceutical additives, preferably 75%, more preferably 90% and still more preferably 95%.

The invention further provides a process for the preparation of a compound of formula (i), in which  $R_1$  etc, m and n are as defined above. It will be appreciated that functional groups such as amino, hydroxyl or carboxyl groups present in the various compounds described below, and which it is desired to retain, may need to be in protected forms before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a particular reaction sequence. Suitable protecting groups for such functionality will be apparent to those skilled in the art. For specific details, see Protective Groups in Organic Synthesis, Wiley Interscience, TW Greene. Thus the process for preparing compounds of formula (i) in which  $R_3$  contains an -OH comprises of deprotecting (for example by hydrogenolysis or hydrolysis) a compound of formula (i) in which  $R_3$  contains an appropriate -OP wherein P represents a suitable protecting group (e.g. benzyl or acetate).

It will be appreciated that where a particular stereoisomer of formula (i) is required, this may be obtained by conventional resolution techniques such as high performance liquid chromatography or the synthetic processes herein described may be performed using the appropriate homochiral starting material.

A process for the preparation of a compound of formula (i) comprises reaction of an appropriate sulphonyl chloride of formula (ii) with a suitable amine of formula (iii)

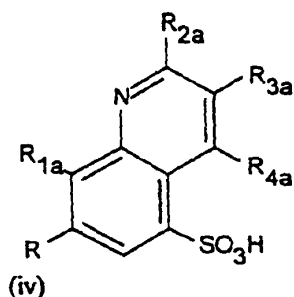


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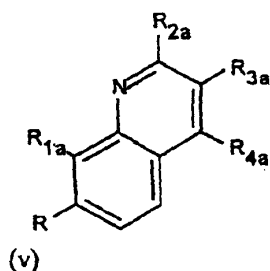
wherein  $R_{1a}$  represents  $R_1$  as defined in relation to formula (i) or a group convertible to  $R_1$  and  $R_{2a}$ - $R_{6a}$  similarly represent  $R_2$ - $R_6$  or groups convertible to  $R_2$ - $R_6$  respectively; and

thereafter, if required, converting any group  $R_{1a}$  to  $R_1$  and/or  $R_{2a}$  to  $R_2$  and/or  $R_{3a}$  to  $R_3$  and/or  $R_{4a}$  to  $R_4$  and/or  $R_{5a}$  to  $R_5$  and/or converting any group  $R_{6a}$  to  $R_6$ . The reaction of a sulphonyl chloride of formula (ii) with an amine of formula (iii) may be carried out under any suitable conditions known to those skilled in the art. Preferably, the reaction is carried out in the presence of a suitable base, for example an amine such as triethylamine, preferably in an appropriate solvent such as dichloromethane. In some cases a stronger base, such as sodium hydride, and a polar solvent such as dimethylformamide, will be required.

Sulphonyl chlorides of formula (ii) are either commercially available, previously described compounds or are prepared using standard procedures known to those skilled in the art. For example, a sulphonyl chloride of formula (ii) is conveniently prepared from the appropriate sulphonic acid (iv)



by treatment with a suitable agent such as thionyl chloride or oxalyl chloride. Alternatively, a sulphonyl chloride of formula (ii) may be prepared by sulphonylation of an appropriate quinoline of formula (v)



with a suitable sulphonylating agent such as chlorosulphonic acid.

Compounds of formula (v) are either commercially-available, previously described compounds or are prepared using standard procedures known to those skilled in the art.,

For example, quinolines of formula (v) may be conveniently prepared by a Skraup reaction (Z.H. Skraup, Ber. 13:2086 (1880)).

A compound of formula (ia) may also be prepared by reaction of a sulphonyl chloride of formula (ii) with an amine of the formula  $H_2NR_{6a}$  (vi), to provide a compound of formula (ia) in which  $R_{3a}$  is H, followed by reaction with an appropriate agent of formula  $R_{4a}Y$  (vii), wherein  $R_{1a}$ - $R_{6a}$  are as defined above and Y represents a suitable leaving group such as halogen. The reaction of a sulphonyl chloride of formula (ii) with an amine of formula (vi) may be carried out under any suitable conditions known to those skilled in the art. Preferably, the reaction is carried out in the presence of a suitable base, for example an amine such as triethylamine, preferably in an appropriate solvent such as dichloromethane. In some cases, a stronger base such as sodium hydride, and a polar solvent such as dimethylformamide, may be required.

The reaction of a compound of formula (ia) in which  $R_{3a}$  is H with an agent of formula (vii) may be carried out under any suitable conditions known to those skilled in the art. Preferably, the reaction is carried out using an appropriate base, such as sodium hydride, preferably in an appropriate solvent such as dimethylformamide. Agents of formula (vii) are either commercially available or are prepared using standard procedures known to those skilled in the art. Agent (vii) can be an alkylating agent such as propyl bromide, an acylating agent such as benzoyl chloride or a sulphonylating agent such as methanesulphonyl chloride.

Amines of formulae (iii) and (vi) are commercially available, previously described compounds or are prepared using standard procedures known to those skilled in the art.

A compound of formula (i) may also be prepared by interconversion of other compounds of formula (i). For example, a compound in which  $R_1$  contains an alkoxy group may be prepared by appropriate alkylation of a compound in which  $R_1$  contains a hydroxy group.

Compounds in which  $R_2$ - $R_4$  contain a CO-alkyl, CO-aryl, CO-heteroaryl, CO-alkylaryl, CO-alkylheteroaryl or CO-alkylheterocyclo group may be prepared from compounds in which  $R_2$ - $R_4$  contain a CN group, by addition of a suitable organometallic agent (such as a Grignard reagent).

By way of further example, compounds in which  $R_2$ - $R_4$  contain an oxime may be prepared from compounds in which  $R_2$ - $R_4$  contain a carbonyl group. This transformation

may be carried out using any appropriate standard conditions known to those skilled in the art. Compounds of formula (i) in which  $R_2-R_4$  contain a carbonyl group may be reduced using standard conditions known to those skilled in the art (for example with sodium borohydride in an appropriate solvent) to provide compounds in which  $R_2-R_4$  contains an alcohol group. Compounds in which  $R_2-R_4$  is alkyl may be prepared by reduction of compounds in which  $R_2-R_4$  is CO-alkyl using standard conditions known to those skilled in the art (for example hydrazine hydrate in the presence of a suitable base in an appropriate solvent). Other transformations may be carried out on compounds of formula (i) in which  $R_2-R_4$  contains a carbonyl group. Such transformations include, but are not limited to, reductive amination and alkylation. Any of the above transformations may be carried out either at the end of the synthesis or on an appropriate intermediate.

A compound of formula (i) or where appropriate a pharmaceutically-acceptable salt thereof and/or a pharmaceutically-acceptable solvate thereof, may be administered *per se* or, preferably, as a pharmaceutical composition also comprising a pharmaceutically-acceptable carrier.

Accordingly, the present invention provides a pharmaceutical composition comprising a compound of formula (i) or where appropriate a pharmaceutically-acceptable salt thereof and/or a pharmaceutically-acceptable solvate thereof, and a pharmaceutically-acceptable carrier.

The active compound may be formulated for administration by any suitable route, the preferred route depending upon the disorder for which treatment is required, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.

The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc, the compounds of the invention are effective in the treatment of humans.

The compositions of the invention may be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid

preparations such as oral or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose.

5 Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers for example microcrystalline cellulose, lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate; disintegrants, for example starch,  
10 polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically-acceptable wetting agents such as sodium lauryl sulphate.

The solid oral compositions may be prepared by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers.

15 Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable  
20 vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia, non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated  
25 coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

Compositions may also suitably be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a nebuliser, or as a microfine powder for  
30 insufflation, alone or in combination with an inert carrier such as lactose. In such a case the particles of active compound suitably have diameters of less than 50  $\mu\text{m}$ , such as from 0.1 to 50  $\mu\text{m}$ , preferably less than 10  $\mu\text{m}$ , for example from 1 to 10  $\mu\text{m}$ , 1 to 5  $\mu\text{m}$  or from

2 to 5  $\mu\text{m}$ . Where appropriate, small amounts of other anti-asthmatics and bronchodilators for example sympathomimetic amines such as isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine; corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

- 5 For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.
- 10 Advantageously, adjuvants such as local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be
- 15 accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

- 20 Compounds of formula (i), or if appropriate a pharmaceutically-acceptable salt thereof and/or a pharmaceutically-acceptable solvate thereof, may also be administered as a topical formulation in combination with conventional topical excipients.

- Topical formulations may be presented as, for instance, ointments, creams or lotions, impregnated dressings, gels, gel sticks, spray and aerosols, and may contain
- 25 appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions.

- Suitable cream, lotion, gel, stick, ointment, spray or aerosol formulations that may
- 30 be used for compounds of formula (i) or if appropriate a pharmaceutically-acceptable salt thereof, are conventional formulations well known in the art, for example, as described in

standard text books such as Harry's Cosmeticology published by Leonard Hill Books, Remington's Pharmaceutical Sciences, and the British and US Pharmacopoeias.

Suitably, the compound of formula (i), or if appropriate a pharmaceutically-acceptable salt thereof, will comprise from about 0.5 to 20% by weight of the formulation, 5 favourably from about 1 to 10%, for example 2 to 5%.

The dose of the compound used in the treatment of the invention will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and the relative efficacy of the compound. However, as a general guide suitable unit doses may be 0.1 to 1000mg, such as 0.5 to 200, 0.5 to 100 or 0.5 to 10mg, for example 0.5, 1, 2, 3, 4 or 5mg; 10 and such unit doses may be administered more than once a day, for example 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day, so that the total daily dosage for a 70kg adult is in the range of about 0.1 to 1000mg, that is in the range of about 0.001 to 20 mg/kg/day, such as 0.007 to 3, 0.007 to 1.4, 0.007 to 0.14 or 0.01 to 0.5mg/kg/day, for example 0.01, 0.02, 0.04, 0.05, 0.06, 0.08, 0.1 or 0.2 mg/kg/day, and such therapy may 15 extend for a number of weeks or months.

When used herein the term "pharmaceutically-acceptable" encompasses materials suitable for both human and veterinary use.

The following Examples illustrate the invention.

**Intermediate 1      8-Methoxyquinoline-5-(N-benzyl)sulphonamide**

20      Triethylamine (0.38ml) was carefully added to a suspension of 8-methoxyquinoline-5-sulphonyl chloride (203mg) in dichloromethane (10ml) at 0°C under nitrogen. Benzylamine (90 µl) was then added and the mixture stirred for 30 minutes at 0°C and 16 hours at room temperature. The reaction was diluted with dichloromethane (30ml), washed with water (15ml) and saturated aqueous sodium chloride (20ml). The 25 organic layer was dried over magnesium sulphate, filtered and the filtrate evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 2% methanol in dichloromethane to yield the titled compound as a white solid (135mg).  
Mp 150-151°C

**Example 1      8-Methoxyquinoline-5-(N-benzyl-N-methanesulphonyl)sulphonamide**

30      Sodium hydride (120mg, 60% dispersion in oil) was added to a solution of 8-methoxyquinoline-5-(N-benzyl)sulphonamide (120mg) in anhydrous DMF (3ml) at 0°C under nitrogen. The resultant mixture was stirred for 20 minutes and then treated with

methanesulphonyl chloride (34 $\mu$ l). The reaction was stirred for one hour at 0°C and 18 hours at room temperature. Water (1ml) was carefully added and the solvent evaporated *in vacuo*. The residue was partitioned between dichloromethane (20ml) and saturated aqueous sodium hydrogen carbonate solution (10ml). The aqueous layer was extracted  
5 with dichloromethane (10ml). The organic extracts were combined and washed with saturated aqueous sodium chloride (10ml), dried over magnesium sulphate, filtered and the filtrate evaporated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with 10% ethyl acetate in dichloromethane to yield the title compound as a white solid (99mg) after trituration with diethyl ether.

10 TLC R<sub>f</sub> 0.45 (5% methanol in dichloromethane)  
Mp 157-158°C

**Example 2 8-Methoxyquinoline-5-(N-benzyl-N-propyl)sulphonamide**

The title compound was obtained as a colourless gum (250mg) from 8-methoxyquinoline-5-(N-benzyl)sulphonamide and bromopropane using a similar procedure  
15 to that described in Example 1.

TLC R<sub>f</sub> 0.1 (50% ethyl acetate in hexane).

**Assay methods**

The assays used to confirm the phosphodiesterase IV inhibitory activity of compounds of formula (i) are standard assay procedures as disclosed by Schilling *et al*,  
20 Anal. Biochem. 216:154 (1994), Thompson and Strada, Adv. Cycl. Nucl. Res. 8:119 (1979) and Gristwood and Owen, Br. J. Pharmacol. 87:91P (1986).

Compounds of formula (i) have exhibited activity at levels consistent with those believed to be useful in treating phosphodiesterase IV-related disease states in those assays.

25 The ability of compounds of formula (i) to inhibit TNF production in human peripheral blood mononuclear cells (PMBC's) is measured as follows. PMBC's are prepared from freshly taken blood or "Buffy coats" by standard procedures. Cells are plated out in RPMI1640 +1% foetal calf serum in the presence and absence of inhibitors. LPS (100 ng/ml) is added and cultures are incubated for 22 h at 37°C in an atmosphere  
30 of 95% air/5% CO<sub>2</sub>. Supernatants are tested for TNF $\alpha$  by ELISA using commercially available kits.



*In vivo* activity in a skin eosinophilia model is determined by using the methods described by Hellewell *et al*, Br. J. Pharmacol. 111:811 (1994) and Br. J. Pharmacol. 110:416 (1993). Activity in a lung model is measured using the procedures described by Kallos and Kallos, Int. Archs. Allergy Appl. Immunol. 73:77 (1984), and Sanjar *et al*, Br. J. Pharmacol. 99:679 (1990).

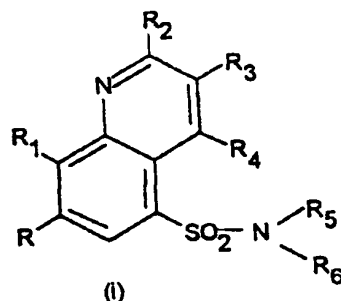
An additional lung model, which allows measurement of inhibition of the early and late-phase asthmatic responses and also the inhibition of airway hyperreactivity, is described by Broadley *et al*, Pulmonary Pharmacol. 7:311 (1994), J. Immunological Methods 190:51 (1996) and British J. Pharmacol. 116:2351 (1995).

10 Abbreviations

LPS	Lipopolysaccharide (endotoxin)
ELISA	Enzyme linked immunosorbent assay

**CLAIMS**

1. A compound of the general formula (i)



wherein R is H, halogen or alkyl;

$R_1$  represents OH, alkoxy optionally substituted with one or more halogens, or thioalkyl;

$R_2$ ,  $R_3$  and  $R_4$  are the same or different and are each H,  $R_7$ ,  $OR_{11}$ ,  $COR_7$ ,  $C(=NOR_7)R_7$ , alkyl- $C(=NOR_7)R_7$ , alkyl- $C(=NOH)R_7$ ,  $C(=NOH)R_7$ , halogen,  $CF_3$ , CN,  $CO_2H$ ,  $CO_2R_{11}$ ,  $CONH_2$ ,  $CONHR_7$ ,  $CON(R_7)_2$ ,  $NR_9R_{10}$  or  $CONR_{12}R_{13}$  where  $NR_{12}R_{13}$  is a heterocyclic ring optionally substituted with one or more  $R_{15}$ ;

$R_5$  represents H, arylalkyl, heteroarylalkyl,  $S(O)_mR_{11}$  or alkyl optionally substituted with one or more substituents chosen from hydroxy, alkoxy,  $CO_2R_8$ ,  $SO_2NR_{12}R_{13}$ ,  $CONR_{12}R_{13}$ , CN, carbonyl oxygen,  $NR_9R_{10}$ ,  $COR_{11}$  and  $S(O)_nR_{11}$ ;

$R_6$  represents aryl, heteroaryl, arylalkyl or heteroarylalkyl;

in  $R_5$  and/or  $R_6$ , the aryl/heteroaryl portion is optionally substituted with one or more substituents alkyl- $R_{14}$  or  $R_{14}$ ;

$R_7$  represents  $R_{11}$  optionally substituted at any position with one or more  $R_{16}$ ;

$R_8$  represents H, alkyl, cycloalkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

$R_9$  represents H, aryl, heteroaryl, heterocyclo, alkyl, cycloalkyl, arylalkyl, heteroarylalkyl, heterocycloalkyl, alkylcarbonyl, alkoxy carbonyl, arylsulphonyl, heteroarylsulphonyl, heterocyclo sulphonyl, arylcarbonyl, heteroarylcarbonyl, heterocyclocarbonyl or alkylsulphonyl;

$R_{10}$  represents H, aryl, heteroaryl, heterocyclo, alkyl, cycloalkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;

$R_{11}$  represents alkyl, cycloalkyl, aryl, heteroaryl, heterocyclo, arylalkyl, heteroarylalkyl or heterocycloalkyl;

$R_{12}$  and  $R_{13}$  are the same or different and are each H or  $R_{11}$ , or  $NR_{12}R_{13}$  represents a heterocyclic ring as defined above;

5  $R_{14}$  represents alkyl (optionally substituted by one or more halogens), cycloalkyl, aryl, heteroaryl, heterocyclo, hydroxy, alkoxy (optionally substituted by one or more halogens), thioalkyl, aryloxy, heteroaryloxy, heterocycloxy, arylalkyloxy, heteroarylalkyloxy, heterocycloalkyloxy,  $CO_2R_8$ ,  $CONR_{12}R_{13}$ ,  $SO_2NR_{12}R_{13}$ , halogen, -CN,  $-NR_9R_{10}$ ,  $COR_{11}$ ,  $S(O)_mR_{11}$ , or carbonyl oxygen;

10  $R_{15}$  represents alkyl, arylalkyl or heteroarylalkyl;

$R_{16}$  represents alkyl, OH,  $OR_{11}$ ,  $NR_9R_{10}$ , CN,  $CO_2H$ ,  $CO_2R_{11}$ ,  $CONR_{12}R_{13}$  or  $COR_{11}$ ;

$m$  is an integer of up to 2; and

$n$  represents 0-2;

15 or a pharmaceutically-acceptable salt thereof.

2. A compound of claim 1, wherein R is H or halogen.

3. A compound of claim 1 or claim 2, wherein  $R_1$  is alkoxy optionally substituted with one or more halogens.

4. A compound of any preceding claim, wherein  $R_2$ ,  $R_3$ ,  $R_4$  are the same or different  
20 and each represent H,  $CF_3$ ,  $COR_7$ ,  $C(=NOR_7)R_7$ ,  $C(=NOH)R_7$ , CN,  $R_7$ , alkyl- $C(=NOH)R_7$ , or alkyl- $C(=NOR_7)R_7$ .

5. A compound of any preceding claim, wherein  $R_5$  is H, arylalkyl, heteroarylalkyl,  $S(O)_mR_{11}$  or alkyl.

6. A compound of any preceding claim, wherein  $R_6$  is arylalkyl or heteroaryl in which  
25 the aryl and heteroaryl portions may be optionally substituted with one or more substituents alkyl- $R_{14}$  or  $R_{14}$ .

7. A compound of claim 1, wherein

R is H;

$R_1$  is optionally-substituted alkoxy;

30  $R_2$ ,  $R_3$  and  $R_4$  are independently H,  $R_7$  or alkyl- $R_7$ ;

$R_7$  is H, OH, alkoxy, aryloxy, heteroaryloxy, heterocycloxy, arylalkoxy, heteroarylalkoxy, heterocycloalkoxy, alkylamino,  $CF_3$  or  $R_{11}$ ;

- $R_4$  is H, alkyl, arylalkyl, heteroarylalkyl or heterocycloalkyl;  
 $R_9$  is not cycloalkyl;  
 $R_{10}$  is not cycloalkyl;  
 $R_{11}$  is not cycloalkyl; and  
5  $R_{14}$  is not alkyl, substituted alkoxy, thioalkyl, or cycloalkyl.
8. A compound of claim 1, which is  
8-methoxyquinoline-5-(N-benzyl-N-methanesulphonyl)sulphonamide.
9. A compound of claim 1, which is  
8-methoxyquinoline-5-(N-benzyl-N-propyl)sulphonamide.
- 10 10. A compound of any preceding claim, in the form of an enantiomer or mixture of enantiomers.
11. A pharmaceutical composition for therapeutic use comprising a compound of any preceding claim and a pharmaceutically-acceptable carrier or excipient.
12. Use of a compound of any of claims 1 to 10, for the manufacture of a medicament  
15 for use in the treatment of a disease state capable of being modulated by inhibition of phosphodiesterase IV or Tumour Necrosis Factor.
13. The use of claim 12, wherein the disease state is a pathological condition associated with a function of phosphodiesterase IV, eosinophil accumulation or a function of the eosinophil.
- 20 14. The use of claim 13, wherein the pathological condition is selected from asthma, chronic bronchitis, chronic obstructive airways disease, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, psoriasis, rheumatoid arthritis, gouty arthritis and other arthritic conditions, ulcerative colitis, Crohn's disease, adult respiratory distress  
25 syndrome, diabetes insipidus, keratosis, atopic eczema, atopic dermatitis, cerebral senility, multi-infarct dementia, senile dementia, memory impairment associated with Parkinson's disease, depression, cardiac arrest, stroke and intermittent claudication.
15. The use of claim 13, wherein the pathological condition is selected from chronic bronchitis, allergic rhinitis and adult respiratory distress syndrome.
- 30 16. The use of claim 12, wherein the disease state is capable of being modulated by TNF inhibition.

17. The use of claim 16, wherein the disease state is an inflammatory disease or autoimmune disease.
18. The use of claim 17, wherein the disease state is selected from joint inflammation, arthritis, rheumatoid arthritis, rheumatoid spondylitis and osteoarthritis, sepsis, septic  
5 shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, pulmonary sarcoidosis, asthma, bone resorption diseases, reperfusion injury, graft vs host reaction, allograft rejection, malaria, myalgias, HIV, AIDS, ARC, cachexia, Crohn's disease, ulcerative colitis, pyresis, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes  
10 mellitus, psoriasis, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, inflammatory bowel disease and leukaemia.
19. The use of claim 14 or claim 18, wherein the pathological condition or disease state is asthma.
20. The use of claim 18, wherein the disease state is acute respiratory distress  
15 syndrome, pulmonary inflammatory disease or pulmonary sarcoidosis.
21. The use of claim 18, wherein the disease state is joint inflammation.
22. The use of claim 13 or claim 17, wherein the disease state is a disease or disorder of the brain, such as brain trauma, stroke, ischaemia, Huntingdon's disease or tardive dyskinesia.
- 20 23. The use of claim 16, wherein the disease state is a yeast or fungal infection.
24. Use of a compound of any of claim 1 to 10, for the manufacture of a medicament for use in gastroprotection.
25. Use of a compound of any of claims 1 to 10, for the manufacture of a medicament for use as an analgesic, anti-tussive or anti-hyperalgesic in the treatment of neurogenic  
25 inflammatory disease associated with irritation and pain.
26. Use of a compound of any of claims 1 to 10, in coadministration with another drug such as a bronchodilator, steroid or xanthine, for asthma therapy.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/01360

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C070215/36 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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# INTERNATIONAL SEARCH REPORT

International Application No  
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International Application No

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